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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 : A61K 31/565, 31/57 — A1

(11) International Publication Number: WO 95/04536

(43) International Publication Date: 16 February 1995 (16.02.95)

(21) International Application Number: PCT/EP94/02513

(22) International Filing Date: 28 July 1994 (28.07.94)

(30) Priority Data:
93202304.7 4 August 1993 (04.08.93) EP

(34) Countries for which the regional or international application was filed: NL et al.

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(81) Designated States: AM, AU, BB, BG, BR, BY, CA, CN, CZ, FI, GE, HU, JP, KG, KP, KR, KZ, LK, LT, LV, MD, MG, MN, NO, NZ, PL, RO, RU, SI, SK, TJ, TT, UA, US, UZ, VN, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG), ARIPO patent (KE, MW, SD).

Published

With international search report.

Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.

(54) Title: ANTIGLUCOCORTICOID STEROIDS FOR THE TREATMENT OF ANXIETY DISORDERS

(57) Abstract

The invention relates to the use of antiglucocorticoid steroids for the manufacture of a pharmaceutical composition for the treatment of anxiety disorders.

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ANTIGLUCOCORTICOID STEROIDS FOR THE TREATMENT OF ANXIETY DISORDERS

The invention relates to the use of antiglucocorticoid steroids for the manufacture of a pharmaceutical composition for the treatment of anxiety disorders.

Antiglucocorticoid steroids are a well known group of steroids which exhibits affinity for the glucocorticoid receptor (GR) and reduce completely or to a considerable extent the action of cortisol. For example, 11ß-substituted steroids having antiglucocorticoid activity are disclosed in EP-A-190759 and EP-A-57115. Other steroids having antiglucocorticoid activity are 10ß-substituted steroids as disclosed in EP-A-188396.

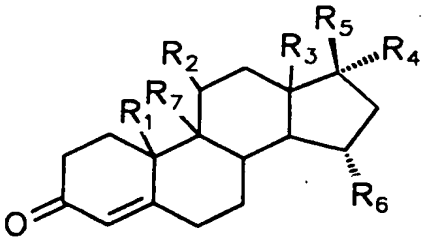
It has now been found that antiglucocorticoid steroids also exert anxiolytic effects, which make these steroids useful for the treatment of anxiety disorders. Anxiety disorder is a rather broad concept including for instance general anxiety, panic disorder, and various kinds of withdrawal symptoms (see: Diagnostic and Statistical Manual of Mental Disorders, 3 RD ED DSM-III, Washington, American Psychiatric Ass., p. 225-239, 1980).
The aim of this invention is to provide a pharmaceutical composition which can be used for the treatment or prevention of anxiety disorders.

Steroids that can be used for the treatment of anxiety disorders are known from WO 9303732. These steroids, however, have no hormonal effects and have no affinity to the glucocorticoid receptor: they activate the GABA

receptor/chloride ionophore complex instead. No hint or suggestion towards the use of antiglucocorticoid steroids for the treatment or prevention of anxiety disorders is made in said publication. Antidepressant activity was suggested by De Kloet et al. (Neuro-endocrinology, 47 (1988), 109 -115) and by Veldhuis et al. (Eur. J. Pharmacol., 115 (1985)211-217). However, since there is no relation between antidepressant and anxiolytic effects, no activity of antiglucocorticoid steroids for treating of preventing anxiety was suggested.

Benzodiazepines, such as librium and valium, are the most commonly used drugs for the treatment of anxiety disorders. However, these compounds are no steroids.

In a preferred embodiment of the invention the antiglucocorticoid steroids according to the invention are 11ß- or 10ß-sustituted steroids having the general formula:



wherein:

R_1 is H, CH_3, unsubstituted or OH or halogen substituted CH_2=CH-CH_2 or CH≡C-CH_2, or an aryl, arylthio or arylmethyl group, the aryl moieties of which may optionally be substituted with (C1-C6) alkyl, (C1-C6) alkoxy, OH, halogen or CF_3, or R_1 together with R_7 is a bond;

R_2 is H, (C1-C6) alkyl or an aryl group optionally substituted with a group selected from (C1-C6) acyl, (C1-C6) alkoxy, (C1-C6) thioalkoxy, $-O-(CH_2)_n-O-$, n being 1 or 2, and $-N(X)(Y)$, X and Y each being independently H or a group selected from (C1-C6) alkyl and (C1-C6) acyl, or R_2 together with R_7 is a bond;

R_3 is (C1-C6) alkyl;

R_4 is H, OH, (C1-C6) alkoxy, (C1-C6) acyloxy, a group selected from (C1-C6) alkyl, (C1-C6) alkenyl and (C1-C6) alkynyl, each of which group may be substituted with hydroxy, oxo, halogen, azido or cyano, or -C≡C-phenyl, the phenyl group of which may optionally be substituted with $-S(O)m-$(C1-C6) alkyl, m being 1 or 2, or with $-N(X)(Y)$, X and Y each being independently H or a group selected from (C1-C6) alkyl and (C1-C6) acyl, or X and Y together with the nitrogen to which they are bonded form a ring;

R_5 is OH or a group selected from (C1-C6) acyloxy, (C1-C6) alkoxy or (C1-C6) acyl, each of which group may optionally be substituted with hydroxy, (C1-C6) alkoxy, (C1-C6) acyloxy or halogen; or

R_4 and R_5 together with the carbon atom to which they are bonded form a 5- or 6-membered ring system;

R_6 is H or methyl optionally substituted with hydroxy or (C1-C6) alkoxy;

R_7 forms a bond with either R_1 or R_2.

In a more preferred embodiment the steroids have above-mentioned formula wherein R_1 together with R_7 is a bond, R_2 represents a phenyl group which is substituted in the para position with an amino group $-N(X)(Y)$, R_3 is methyl or ethyl, R_4 is prop-1-ynyl, R_5 is hydroxy and R_6 is H, hydroxymethyl or methoxymethyl.

In particular 11ß-(4-dimethylaminophenyl)-17ß-hydroxy-17α-(prop-1-ynyl)-estra-4,9-dien-3-one (RU38486) is a preferred steroid.

Other preferred steroids are (11ß,17α)-11,21-bis[4-(dimethylamino)phenyl]-17-hydroxy-19-norpregna-4,9-dien-20-yn-3-one, (11ß,17α)-11-[4-(dimethylamino)phenyl]-17-hydroxy-21-[4-(1-pyrrolidinyl)phenyl]-19-norpregna-4,9-dien-20-yn-3-one, (11ß,17α)-11-(1,3-benzodioxol-5-yl)-21-[4-(dimethylamino)phenyl]-17-hydroxy-19-norpregna-4,9-dien-20-yn-3-one, and (11ß,17α)-11-[4-(dimethylamino)phenyl]-17-hydroxy-21-[4-(methylsulfonyl)phenyl]-19-norpregna-4,9-dien-20-yn-3-one.

The aryl group in the definition of R_1 may be derived from benzene, naphthalene or a 5- or 6-membered heteroaryl which comprises 1 to 4 hetero atoms selected from N, O and S. Preferably the aryl group is phenyl.

In the definition of R_2 the aryl group may be derived from, for example, benzene, biphenyl, naphthalene, anthracene or phenantrene. Phenyl is the preferred group. In particular a phenyl group is preferred, which is substituted in the para position with the $-N<^{X}_{Y}$ group or in the meta position with OCH_3 or SCH_3.

The (C1-C6) alkyl group is a branched or unbranched alkyl group having 1-6 carbon atoms, such as methyl, ethyl, propyl, butyl, isopropyl, pentyl, isopentyl, hexyl, tert-butyl and the like. Preferred alkyl groups have 1-4 carbon atoms; most preferred is the methyl group.

The (C2-C6) alkenyl group is a branched or unbranched alkenyl group having 2-6 carbon atoms, such as vinyl, 2-propenyl, 1,3-butadienyl and the like.

The (C2-C6) alkynyl group is a branched or unbranched alkynyl group having 2-6 carbon atoms, such as ethynyl, propynyl, butynyl, and the like. Most preferred is the prop-1-ynyl group.

The (C1-C6) alkylidene group is a branched or unbranched alkylidene group having 1-6 carbon atoms, such as ethylidene, propylidene, 2-methylpropylidene and the like.

The (C1-C6) alkoxy group is an alkoxy group of which the alkyl moiety is the (C1-C6) alkyl group as previously defined.

The (C1-C6) thioalkoxy group is an -S-alkyl group of which the alkyl moiety is the (C1-C6) alkyl group as previously defined.

The arylthio and arylmethyl groups, are arylthio and arylmethyl groups the aryl moiety of which is derived from benzene, naphthalene or a 5- or 6-membered heteroaryl which comprises 1 to 4 hetero atoms selected from N, O and S. Preferably the aryl moiety is phenyl.

The (C1-C6) acyl group is a branched or unbranched acyl group having 1-6 carbon atoms, such as formyl, acetyl, propionyl, butyryl and the like.

The (C1-C6) acyloxy group is a branched or unbranched acid ester group derived from a carboxylic acid having 1-6 carbon atoms, such as the ester group derived from formic acid, acetic acid, propionic acid and the like.

The term halogen means Cl, Br, F, or I. In particular F and Cl are preferred halogens.

When X and Y together with the nitrogen to which they are bonded form a ring, this ring is a saturated 5- or 6-membered ring, which may comprise a second hetero-atom selected from N, O and S. Examples are pyrrolidinyl, piperidinyl, piperazinyl, and morpholinyl.

When R_4 and R_5 together represent a 5- or 6-membered ring system, this ring system can be a homo- or heterocyclic ring system with 5 or 6 atoms in the ring, the carbon atom at position 17 of the steroid skeleton being one of these 5 or 6 atoms. Preferably the ring system comprises at least one oxygen atom in the ring which oxygen atom is bonded to the carbon atom at position 17 of the steroid skeleton. In particular 5-membered heterocyclic ring systems having the following structures are preferred:

wherein
the carbon atom which is provided with an * being the carbon atom in position 17 of the steroid skeleton, and X is H_2, [H,(C1-C6) acyloxy], [H,(C1-C6) hydrocarbyl] or oxygen. (C1-C6) hydrocarbyl means a hydrocarbon group having 1-6 carbon atoms such as (C1-C6) alkyl, (C1-C6) alkenyl, or (C1-C6) alkynyl, as previously defined.

The antiglucocorticoid steroids according to the invention can be prepared by suitable techniques known in the art, for example as described in BE-A-862869, DE-OS-3307143, EP-A-188396, EP-A-57115 and J. of Steroid Bioch. 31:567-571 (1988), which are incorporated by reference.

The antiglucocorticoid steroids according to the invention can be administered enterally or parentally, and for humans preferably in a daily dosage of 0,001-10 mg per kg body weight. Mixed with pharmaceutically suitable auxiliaries, e.g. as described in the standard reference, Genarro et al., Remington's Pharmaceutical Sciences, (18th ed., Mack Publishing Company, 1990, see especially Part 8: Pharmaceutical preparations and their manufacture), the steroids may be compressed into solid dosage units, such as pills, tablets, or be processed into capsules or suppositories. By means of pharmaceutically suitable liquids the steroids can also be applied as an injection preparation in the form of a solution, suspension, emulsion, or as a spray, e.g. a nasal spray. For making dosage units, e.g. tablets, the use of conventional additives such as fillers, colorants, polymeric binders and the like is contemplated. In general any pharmaceutically acceptable additive which does not interfere with the function of the active compounds can be used.
Suitable carriers with which the compositions can be administered include lactose, starch, cellulose derivatives and the like, or mixtures thereof, used in suitable amounts.

The invention is further illustrated by the following examples without being limited thereto.

Example 1: Antagonism of stress induced hyperthermia

Rectal temperature measurement induces a stress reaction, which results in a rise in body temperature. This rise in temperature can be inhibited by anxiolytic drugs. The rise in temperature after treatment with a drug, expressed as percentage of the rise in temperature after treatment with a placebo, is an indication for the anxiolytic effect of the compound. Animals are pre-treated with reserpine to lower their body temperature

and make the stress induced temperature rise more apparent.

1.1 Animals

Male mice (Crl: CD-1 (ICR) BR, from Charles River, Germany) weighing 20-30 g were used. They were kept in a temperature controlled room (21-23°C) under a fixed 12 h light-dark cycle. Food pellets and drinking solution were available ad libitum.

1.2 Measurement of rectal temperature

The body temperature was measured per rectum using an electrothermometer (Ellab TE3, Electrolaboratoriet, Copenhagen, Denmark), lubricated with Vaseline grease. The probe was inserted to a depth of approximately 2.5 cm and left until the temperature indication was constant.

1.3 Drugs

The drugs used were RU38486; 11ß-(4-dimethylaminophenyl)-15α-hydroxymethyl-17α-(prop-1-ynyl)-17ß-hydroxyestra-4,9-dien-3-one (A); 11ß-(4-dimethylaminophenyl)-15α-methoxymethyl-17α-(prop-1-ynyl)-17ß-hydroxy-estra-4,9-dien-3-one (B); (11ß,17α)-11,21-bis[4-(dimethylamino)phenyl]-17-hydroxy-19-norpregna-4,9-dien-20-yn-3-one (C); (11ß,17α)-11-[4-(dimethylamino)phenyl]-17-hydroxy-21-[4-(1-pyrrolidinyl)phenyl]-19-norpregna-4,9-dien-20-yn-3-one (D); (11ß,17α)-11-(1,3-benzodioxol-5-yl)-21-[4-(dimethylamino)phenyl]-17-hydroxy-19-norpregna-4,9-dien-20-yn-3-one (E); and (11ß,17α)-11-[4-(dimethylamino)phenyl]-17-hydroxy-21-[4-(methylsulfonyl)-phenyl]-19-norpregna-4,9-dien-20-yn-3-one (F). Drugs were used in dosages between 0.32 mg/kg and 32 mg/kg. For comparison librium and valium were used in dosages of 1 mg/kg, 3.2 mg/kg and 10 mg/kg. The drugs were dissolved in mulgophen/NaCl and administered at a volume of 10 ml/kg.

1.4 Procedure

The mice were pretreated with 2 mg/kg (s.c.) of reserpine (monoamine depletor). The reserpine induced a decrease in body temperature. After 17 hours the body temperature was measured rectally, which gave the baseline value. Thirty minutes after baseline measurement the drugs were administered subcutaneously and at t = 30, 60, 120, 180, and 240 min the temperature was measured. The rise in temperature at t = 120 min and at t = 240 min due to the stress reaction was expressed as percentage of the temperature rise of the placebo at t = 120 min and t = 240 min respectively. These percentages are presented in Table 1.

	dosage in mg/kg				
	0.32	1	3.2	10	32
RU38486	-	-	70(98)	83(89)	71(74)
steroid A	-	-	42(58)	48(54)	66(71)
steroid B	-	-	63(32)	67(38)	49(37)
steroid C	33(50)	57(94)	11(9)	-	-
steroid D	102(102)	61(85)	84(109)	-	-
steroid E	73(97)	59(91)	57(104)	-	-
steroid F	84(87)	58(43)	115(127)	-	-
librium	-	67(69)	48(87)	33(30)	-
valium	-	20(3)	7(2)	37(11)	-

Table 1: *Temperature rise in mice after treatment with antiglucocorticoid steroids, expressed as percentage of the rise in temperature observed after treatment with a placebo. The rise in temperature is measured at t = 120 (between brackets the temperature rise at t = 240 min) at various dosages of drugs administered.*

As can be seen from the results of Table 1, the antiglucocorticoid steroids considerably reduce the rise in temperature. The observed effect on the stress

reaction is comparable to the effect resulting from treatment with librium and valium respectively.

Example 2: Anxiety test

The (Borsini) anxiety test (Psychopharmacology 98:207-211, 1989) is based on the fact that among animals from the same cage, those removed last have a higher body temperature as compared to those removed first. This phenomenon can also be observed by reversing the order of removal of the animals from the cage and can therefore be interpreted as an indication of a state of anxiety due to expectation of a (known or unknown) event. The observed rise in body temperature can be prevented by the administration of anxiolytic drugs. This test is useful in demonstrating the anxiolytic effect of compounds.

2.1 Animals

Male mice (Crl: CD-1 (ICR) BR, from Charles River, Germany) weighing 20-30 g were used. They were kept in a temperature controlled room (21-23°C) under a fixed 12 h light-dark cycle. All animals were housed in macrolon cages; 10 animals per cage. Food pellets and water were available ad libitum. Prior to the experiments the animals were allowed to adapt to the environment for at least 14 days.

2.2 Temperature measurement

The body temperature was measured per rectum using an electrothermometer (Ellab TE3, Electrolaboriet, Copenhagen, DK), lubricated with Vaseline grease. The probe was inserted to a depth of approximately 2.5 cm and left until the temperature indication was constant.

2.3 Drugs

The used drug was RU38486 in dosages of 3.2, 10, and 32 mg/kg. RU38486 was dissolved in mulgophen/NaCl and

injected at t = -30 min. The drug was administered at a volume of 10 ml/kg.

2.4 Procedure

The methodology was similar to that described by Borsini et al (Psychopharmacology 98:207-211, 1989). In short, at t = 0 min all mice were injected subcutaneously. At t = 30 min the temperature of the first and the last three mice was measured. Mouse 4 to 7 were simply removed. Furthermore the behavioural activity of mouse 10 was determined by behavioural observations. Effects were evaluated by subtracting the mean body temperature of the first three mice from the mean temperature of the last three mice. Comparison between placebo and treatment group were made by means of Mann Whitney-U tests.

2.5 Results

RU38486 in a dosage of 3.2 mg/kg reduced the temperature difference between the first and the last three mice significantly. The results are presented in Figure 1.

Example 3: Antagonism of the fear potentiated startle

The fear potentiated startle is a well known paradigm to evaluate anxiolytic drugs (Davis, Behavioral Neuroscience 100 (1986) 814-824). In this paradigm rats are trained to associate a light with the presentation of footshocks. Acoustic noise bursts normally elicit a startle reaction; this reaction is increased when the noise burst is presented in the presence of the light. The fear potentiated startle phenomenon can be inhibited by anxiolytics in the non-sedative dose-range.

3.1 Animals

Male rats (Wistars, HSD/Cpb: Wu, Harlan Sprague Dawley, Zeist, The Netherlands) weighing 275 - 300 g were used.

They were housed in groups of 5 (in 40 * 40 * 17 cm cages) at a room temperature of 21 - 23 °C. They were exposed to a normal 12-h light-dark cycle (lights on at 6.00 h) and had free access to food and water.

3.2 Measurement of startle reflexes

The apparatus used was an SRLAB system (San Diego Instruments, San Diego, CA, USA). The system consisted of eight startle boxes, which contained each a cylindrical tube resting on a piezoelectric accelerometer for detecting total body-activity within the Plexiglas tube. Reflex amplitude was measured during the 200 ms interval following the presentation of the stimulus. The acoustic noise bursts (120 dB) and background noise (70 dB) were presented by a loudspeaker, mounted 24 cm above the animal.

For the fear potentiated startle session a stainless steel shock grid, which was power-supplied by a Coulbourn Animal shocker, was placed into each Plexiglas tube.

The startle boxes were sound-tight and isolated from each other. Between test sessions, the cages were cleaned thoroughly using water and non-perfumed soap.

3.3 Drugs

The drug used was RU38486 in a dosages of 3.2 mg/kg. RU38486 was dissolved in mulgophen/NaCl and administered at a volume of 5 ml/kg.

3.4 Procedure

For two days, rats were placed in the startle boxes in which the shock grids were installed. They were conditioned using a session of 15 trials, in which a signal of 3 seconds light was linked to a 1 mA shock during 0.5 s.

On day 3 the animals were injected with the compound or placebo and were placed in the startle boxes 90 min later. They were, after an acclimatisation period of 5

min (background noise only) confronted with 60 acoustic noise bursts (25 ms duration). Bursts were separated by an interval of 15 s. Data were averaged over blocks of 5 trials.

3.5 Results

RU38486 (3.2 mg/kg) reduced the amplitude of the fear potentiated startle. The results are presented in Figure 2.

Example 4:

A pharmaceutical composition based on RU38486 for the treatment of anxiety disorders was prepared and comprises 50 mg of RU38486 and additives (talc, polyvinylpyrrolidone and magnesium stearate) up to a total weight of 120 mg.

Example 5:

(11β,17α)-11,21-Bis[4-(dimethylamino)phenyl]-17-hydroxy-19-norpregna-4,9-dien-20-yn-3-one

a) 27 g (100 mmol) of estra-4,9-diene-3,17-dione, dissolved in 270 ml of tetrahydrofuran (THF) and 270 ml of methanol, were cooled to -10 °C and treated with 2.27 g (60 mmol) of sodium borohydride. The solution was stirred for 30 min at -10 °C. Work-up was accomplished by dropwise addition of 8 ml of 50% acetic acid. The mixture was extracted with ethyl acetate, the organic layers were washed with brine, dried on anhydrous magnesium sulfate, filtered and evaporated to dryness resulting in 27.2 g of 17β-hydroxy-estr-4,9-diene-3-one.
b) 25 g of the obtained material were dissolved in 375 ml of dichloromethane; 125 ml of ethylene glycol, 75 ml of trimethylorthoformate and 250 mg of p-toluenesulfonic acid were added and the mixture was refluxed for 20 min. After cooling, 200 ml of a saturated sodium hydrogen carbonate solution were added and the resulting mixture

was extracted with dichloromethane. Evaporation in vacuo followed by purification of the resulting oil by column chromatography using silicagel, provided 19.9 g of 17α-hydroxy-estra-5(10),9(11)-diene-3-one 3-(cyclic 1,2-ethanediyl acetal) as an oil.

c) 19.9 g (62.9 mmol) of 17α-hydroxy-estra-5(10),9(11)-diene-3-one 3-(cyclic 1,2-ethanediyl acetal) were dissolved in 400 ml of dichloromethane. 27.6 g (336 mmol) of sodium acetate were added followed by 36.2 (168 mmol) of pyridinium chlorochromate and the mixture was stirred at ambient temperature. After 2 hours, 43.5 ml of 2-propanol were added and stirring was continued for 1 hour. The mixture was filtered over celite, evaporated and partitioned between ethyl acetate (1350 ml) and water (675 ml). The organic layer was separated, washed with brine, dried with anhydrous magnesium sulfate and filtered. Evaporation followed by purification by column chromatography using silicagel provided 10.9 g of estra-5(10),9(11)-diene-3,17-dione 3-(cyclic 1,2-ethanediyl acetal). Melting point: 152 °C.

d) A mixture of 13 g (116.2 mmol) of potassium tert. butoxide, 55 ml of THF and 18.7 ml of tert. butanol was cooled to 0-5 °C under inert atmosphere. Acetylene was bubbled through the mixture for one hour; then 9.43 g (30 mmol) of estra-5(10),9(11)-diene-3,17-dione 3-(cyclic 1,2-ethanediyl acetal), dissolved in 50 ml of THF were added. Stirring was continued for 1.5 hrs at 0-5 °C under acetylene atmosphere. Work-up was accomplished by pouring the mixture into a saturated aqueous ammonium chloride solution, followed by ethyl acetate extraction. The organic layers were washed with brine,

dried with anhydrous magnesium sulfate, filtered and evaporated to give 10.4 g of 17α-ethynyl-17β-hydroxy-estra-5(10),9(11)-diene-3-one 3-(cyclic 1,2-ethanediyl acetal).

e) 10 g (29.4 mmol) of 17α-ethynyl-17β-hydroxy-estra-5(10),9(11)-diene-3-one 3-(cyclic 1,2-ethanediyl acetal) were dissolved in 150 ml of dichloromethane. Subsequently 0.91 ml of pyridine, 2.84 ml of trifluoro-acetophenone and 18.8 ml of 30% hydrogen peroxide were added and the resulting two-phase system was vigorously stirred at room-temperature for 36 hrs. The mixture was poured into water and the organic layer was washed twice with a saturated sodium thiosulfate solution. Drying with anhydrous magnesium sulfate, filtering and evaporation provided a semi-solid mass consisting of a mixture of epoxides. Trituration with toluene afforded 4.22 g of 5α,10α-epoxy-17α-ethynyl-17β-hydroxy-estr-9(11)-ene-3-one 3-(cyclic 1,2-ethanediyl acetal).

f) 158 mg of CuCl were added at 0-5 °C to a solution of p-dimethylaminophenylmagnesium bromide in THF, prepared from 1.49 g of magnesium (61 mmol), 30 ml of THF and 11.8 g (58.9 mmol) of 4-bromo-N,N-dimethylaniline. After stirring for 30 min at 0-5 °C, 4.2 g of 5α,10α-epoxy-17α-ethynyl-17β-hydroxy-estr-9(11)-ene-3-one 3-(cyclic 1,2-ethanediyl acetal) in 42 ml of THF were added dropwise. After being stirred for 2.5 hrs at ambient temperature, the solution was poured into a saturated ammonium chloride solution and extracted with ethyl acetate. The organic layers were washed until neutral, dried with anhydrous magnesium sulfate, filtered and evaporated in vacuo and the residue was chromatographed

using silicagel. This provided after crystallization from ether/heptane 3.2 g of pure 5α,17β-dihydroxy-11β-[4-(N,N-dimethylamino)phenyl]-17α-ethynyl-estr-9-ene-3-one 3-(cyclic 1,2-ethanediyl acetal). Melting point: 198 °C.

g) 3.0 g (6.3 mmol) of 5α,17β-dihydroxy-11β-[4-(N,N-dimethylamino)phenyl]-17α-ethynyl-estr-9-ene-3-one 3-(cyclic 1,2-ethanediyl acetal) were dissolved in 39 ml of pyrrolidine. Subsequently 1.26 g of 4-bromo-N,N-dimethylaniline (6.3 mmol), 33 mg of palladium(II) acetate, 33 mg of copper(I) iodide and 99 mg of triphenylphosphine were added and the mixture was refluxed for one hour under inert atmosphere. After cooling, the mixture was poured into a 50% aqueous ammonium chloride solution and extracted with ethyl acetate. The organic layers were washed with brine, dried with anhydrous magnesium sulfate, filtered and evaporated to dryness, yielding a crystalline mass. Trituration with diethyl ether provided 2.45 g of pure 11,21-bis[(dimethylamino)-phenyl]-5α,17β-dihydroxy-pregn-9-ene-20-yn-3-one 3-(cyclic 1,2-ethanediyl acetal). Melting point: 150 °C.

h) 2.45 g (4.0 mmol) of 11,21-bis[(dimethylamino)-phenyl]-5α,17β-dihydroxy-pregn-9-ene-20-yn-3-one 3-(cyclic 1,2-ethanediyl acetal) were dissolved in 123 ml of acetone and with stirring 4.9 ml 6N HCl were added. After stirring for 30 min at ambient temperature, the mixture was neutralized with sodium hydrogen carbonate, followed by extraction with ethyl acetate. The organic layer was washed until neutral, dried with anhydrous magnesium sulfate, filtered and evaporated in vacuo. The residue was purified by column chromatography using silicagel. This afforded 1.2 g of pure (11β,17α)-11,21-bis[4-(dimethylamino)phenyl]-17-hydroxy-19-norpregna-4,9-dien-20-yn-3-one. $[\alpha]^{20}_D$ = -12° (c = 1, chloroform).

Example 6

The following products were prepared from 5α,17β-dihydroxy-11β-[4-(N,N-dimethylamino)phenyl]-17α-ethynyl-estr-9-ene-3-one 3-(cyclic 1,2-ethanediyl acetal) (see example 5f) by using the appropriate starting material for the Heck coupling reaction (according to the procedure of example 5g), followed by the acidic dehydration and deprotection as described in example 5h:

A using 4-bromo-(1-pyrrolidinyl)benzene the reaction resulted in (11β,17α)-11-[4-(dimethylamino)phenyl]-17-hydroxy-21-[4-(1-pyrrolidinyl)phenyl-19-norpregna-4,9-dien-20-yn-3-one having a specific rotation of $[\alpha]^{20}_D$ = -19° (c=1, chloroform).

B using 4-bromo-(methylsulfonyl)benzene the reaction resulted in (11β,17α)-11-[4-(dimethylamino)phenyl]-17-hydroxy-21-[4-(methylsulfonyl)phenyl-19-norpregna-4,9-dien-20-yn-3-one having a specific rotation of $[\alpha]^{20}_D$ = -23° (c=0.5, dioxane).

Example 7

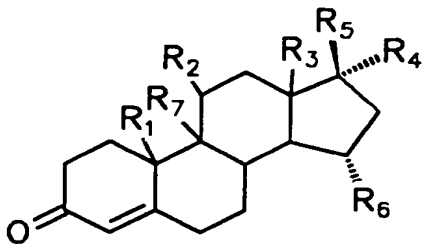
According to the procedure described in example 5f, the Cu-catalyzed Grignard reaction of 3,4-methylenedioxo-phenylmagnesium bromide with 5α,10α-epoxy-17α-ethynyl-17β-hydroxy-estr-9(11)-ene-3-one 3-(cyclic 1,2-ethanediyl acetal) provided 5α,17β-dihydroxy-17α-ethynyl-11β-(1,3-benzodioxol-5-yl)-estr-9-ene-3-one 3-(cyclic 1,2-ethanediyl acetal). Melting point: 155 °C.

By using 4-bromo-N,N,-dimethylaniline for the Heck coupling reaction (according to the procedure of example 5g), followed by the acidic dehydration and deprotection as described in example 5h was prepared (11β,17α)-11-(1,3-benzodioxol-5-yl)-21-[4-(dimethylamino)phenyl]-17-hydroxy-19-norpregna-4,9-dien-20-yn-3-one; $[\alpha]^{20}_D$= -63° (c=1, chloroform).

Claims

1. A use of antiglucocorticoid steroids for the manufacture of a pharmaceutical composition for the treatment of anxiety disorders.

2. The use according to claim 1, characterised in that the antiglucocorticoid steroids have general formula



R_1 is H, CH_3, unsubstituted or OH or halogen substituted CH_2=CH-CH_2 or CH≡C-CH_2, or an aryl, arylthio or arylmethyl group, the aryl moieties of which may optionally be substituted with (C1-C6) alkyl, (C1-C6) alkoxy, OH, halogen or CF_3, or R_1 together with R_7 is a bond;

R_2 is H, (C1-C6) alkyl or an aryl group optionally substituted with a group selected from (C1-C6) acyl, (C1-C6) alkoxy, (C1-C6) thioalkoxy, -O-$(CH_2)_n$-O-, n being 1 or 2, and $-N\begin{matrix}X\\Y\end{matrix}$, X and Y each being independently H or a group selected from (C1-C6) alkyl and (C1-C6) acyl, or R_2 together with R_7 is a bond;

R_3 is (C1-C6) alkyl;

R_4 is H, OH, (C1-C6) alkoxy, (C1-C6) acyloxy, a group selected from (C1-C6) alkyl, (C1-C6) alkenyl and (C1-C6) alkynyl, each of which group may be substituted with hydroxy, oxo, halogen, azido or cyano, or -C≡C-phenyl, the phenyl group of which

may optionally be substituted with -S(O)m-(C1-C6) alkyl, m being 1 or 2, or with -N(X)(Y), X and Y each being independently H or a group selected from (C1-C6) alkyl and (C1-C6) acyl, or X and Y together with the nitrogen to which they are bonded form a ring;

R_5 is OH or a group selected from (C1-C6) acyloxy, (C1-C6) alkoxy or (C1-C6) acyl, each of which group may optionally be substituted with hydroxy, (C1-C6) alkoxy, (C1-C6) acyloxy or halogen; or

R_4 and R_5 together with the carbon atom to which they are bonded form a 5- or 6-membered ring system;

R_6 is H or methyl optionally substituted with hydroxy or (C1-C6) alkoxy;

R_7 forms a bond with either R_1 or R_2.

3. Use according to claim 1 or 2, characterised in that said steroid is selected from 11ß-(4-dimethylamino-phenyl)-17ß-hydroxy-17α-(prop-1-ynyl)-estra-4,9-dien-3-one (RU38486), (11ß,17α)-11,21-bis[4-(dimethyl-amino)phenyl]-17-hydroxy-19-norpregna-4,9-dien-20-yn-3-one, (11ß,17α)-11-[4-(dimethylamino)phenyl]-17-hydroxy-21-[4-(1-pyrrolidinyl)phenyl]-19-norpregna-4,9-dien-20-yn-3-one, (11ß,17α)-11-(1,3-benzodioxol-5-yl)-21-[4-(dimethylamino)phenyl]-17-hydroxy-19-norpregna-4,9-dien-20-yn-3-one, and (11ß,17α)-11-[4-(dimethylamino)phenyl]-17-hydroxy-21-[4-(methyl-sulfonyl)phenyl]-19-norpregna-4,9-dien-20-yn-3-one.

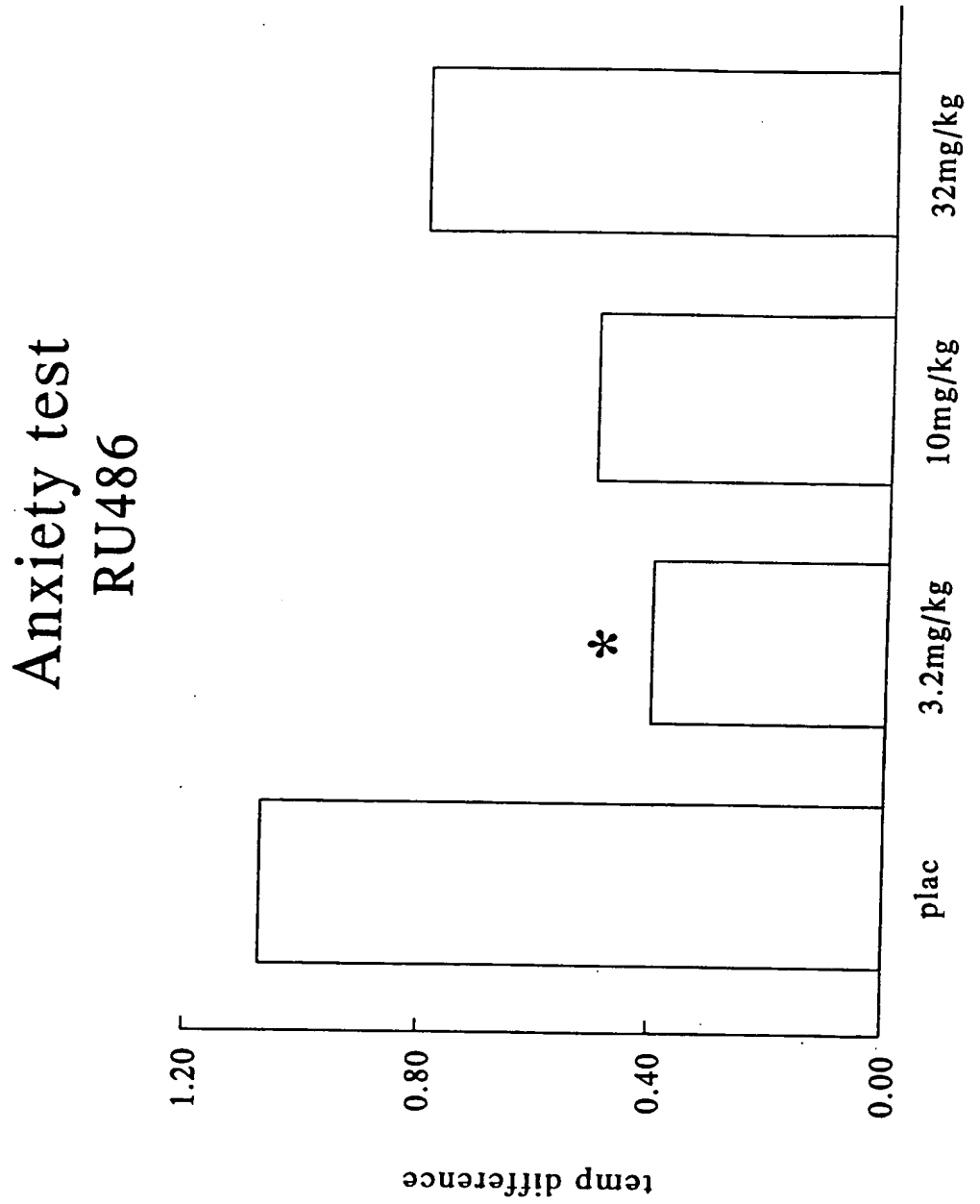


FIGURE 1: ***Temperature difference between the first and last three mice measured at various dosages of RU38486 (p<0.05; see Example 2).***

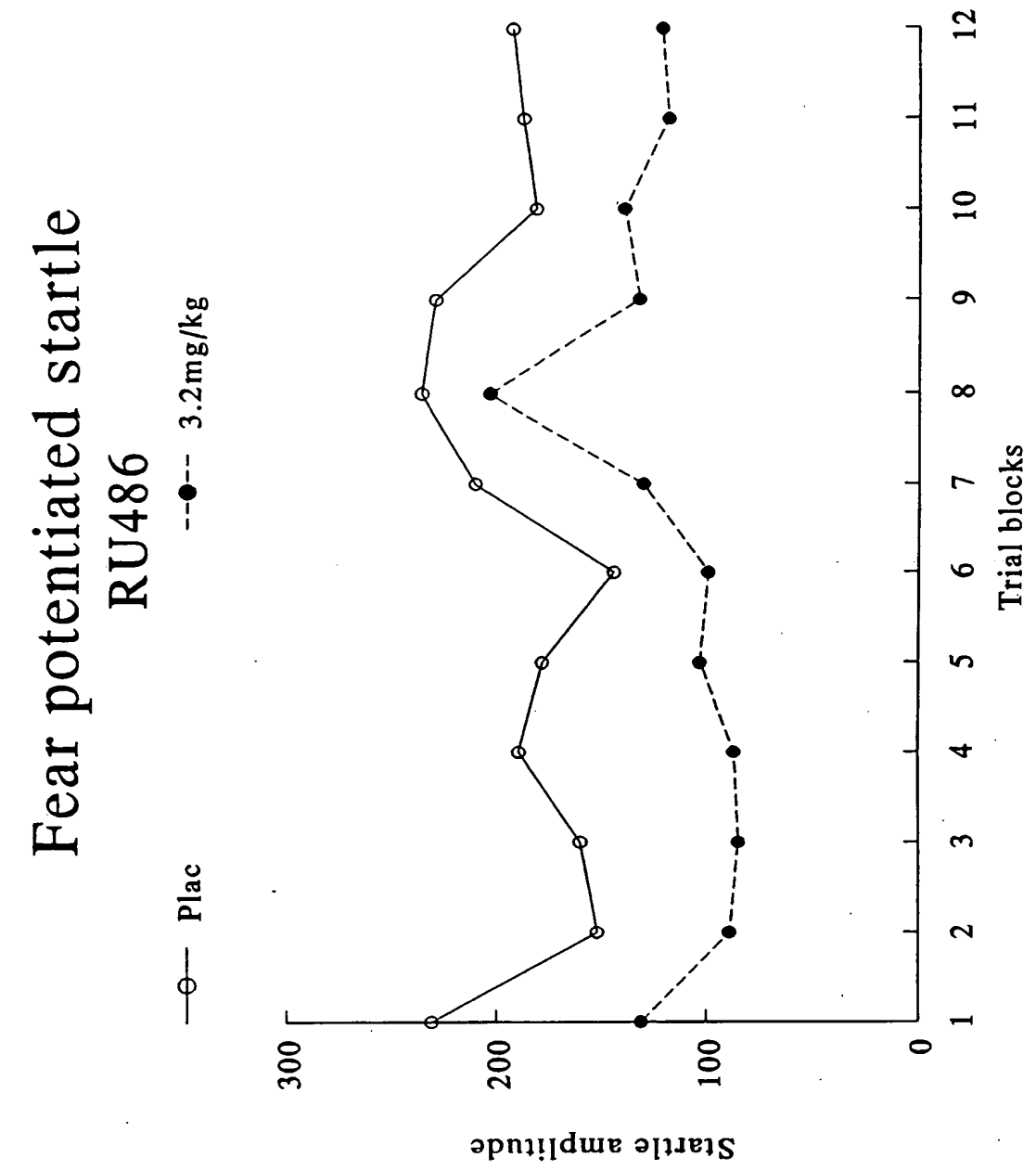


FIGURE 2: ***Fear potentiated startle of the rats measured under placebo (plac) or RU38486 (3.2 mg/kg) conditions (see Example 3).***

INTERNATIONAL SEARCH REPORT

Int tional Application No
PCT/EP 94/02513

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K31/565 A61K31/57

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	NEUROENDOCRINOLOGY, vol.47, no.2, February 1988 pages 109 - 115 DE KLOET, E.R. ET AL 'ANTIGLUCOCORTICOID RU 38486 ATTENUATES RETENTION OF A BEHAVIOUR AND DISINHIBITS THE HYPOTHALAMIC-PITUITARY ADRENAL AXIS AT DIFFERENT BRAIN SITES' cited in the application see the whole document --- -/--	1-3

[X] Further documents are listed in the continuation of box C.

[ ] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
30 November 1994	27. 12. 94

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax (+31-70) 340-3016	Mair, J

Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EUROPEAN JOURNAL OF PHARMACOLOGY, vol.115, no.2-3, 1985 pages 211 - 217 VELDHUIS, H.D. ET AL 'GLUCOCORTICOIDS FACILITATE THE RETENTION OF ACQUIRED IMMOBILITY DURING FORCED SWIMMING' cited in the application see the whole document	1-3
A	HORMONES AND BEHAVIOUR, vol.27, no.2, June 1993 pages 167 - 183 KORTE, S.M. ET AL 'CENTRAL ACTIONS OF CORTICOTROPIN-RELEASING HORMONE (CRH) ON BEHAVIOURAL, NEUROENDOCRINE, AND CARDIOVASCULAR REGULATION: BRAIN CORTICOID RECEPTOR INVOLVEMENT' see the whole document	1-3
A	BRAIN RESEARCH, vol.615, no.2, 2 July 1993 pages 304 - 309 PAPOLOS, D.F. ET AL 'EFFECTS OF THE ANTIGLUCOCORTICOID RU 38486 ON THE INDUCTION OF LEARNED BEHAVIOUR HELPLESS BEHAVIOUR IN SPRAGUE-DAWLEY RATS' see the whole document	1-3

ernational application No.

PCT/EP 94/ 02513

INTERNATIONAL SEARCH REPORT

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☒ Claims Nos.: 2
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

In view of the large number of compounds which are theoretically defined by the formula of claim 2, the search has been restricted on economic grounds to the claimed compounds and the general inventive concept.

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searches without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.